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EXAMINER	
PAGONAKIS, ANNA	
ART UNIT	PAPER NUMBER
1614	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,025	ELCOMBE ET AL.	
	Examiner	Art Unit	
	ANNA PAGONAKIS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8,10,13-15,17-23,25-27,29,31,32 and 34-42* is/are pending in the application.

4a) Of the above claim(s) *7,8,10,14,15,17-23,25,29,31,32 and 34-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,13 and 38-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 sheet, 1/15/2009*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed 1/15/2009 has been received and entered into the present application.

Claims 1, 6-8, 10, 13-15, 17-23, 25-27, 29, 31, 32 and 34-42 are pending. Accordingly, no claims are added, withdrawn, amended or newly added. Claims 7-8, 10, 14-15, 17-23, 25, 29, 31, 32 and 34-37 remain withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b) as being drawn to nonelected subject matter, there being no allowable generic or linking claim.

As reflected by the attached, completed copy form PTO/SB/08A (one page total), the Examiner has considered the cited references.

Applicant's arguments, filed 1/15/2009 have been fully considered. Rejections not reiterated from the previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claims 1, 6, 13 and 38-42 are currently under examination and the subject of this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims **1, 6, 13, 38-42** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427

F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The claims are drawn to a method of administering a composition of PFOA to a patient for the treatment of breast, colon or prostate cancer.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

As illustrative of the state of the art, the examiner cites:

(1) The Jere Beasley Report, A national firm located in Montgomery, Alabama. February 2005.

(2) FDA's Teflon carcinogen warning getting stronger - The Cancer Blog. 2006.

(3) Teflon cancer risks downplayed? www.msnbc.com. 2005.

The first reference, discloses that the EPA is considering whether there is a potential risk of developmental and other adverse effects from exposure to low levels of a chemical used in making the nonstick substance Teflon. The report based on perfluorooctanoic acid and its salts suggests that PFOA could be carcinogenic in rats though the cancer hazard for people is less certain. Further, in the investigation, DuPont, the a manufacturer of Teflon, states there are no known human health effects (positive or negative) caused (pages 39 and 40).

The second reference, discusses that PFOA has been recommended by the EPA to be labeled as a likely carcinogen. The reference discloses that past research in fact has documented that PFOA causes cancer in animals.

The final reference discusses that PFOA is more of a cancer risk than previously indicated by the EPA and that suggestive evidence exists of human carcinogenicity

2. The breadth of the claims

The claims encompass the treatment of breast, colon or prostate cancer by treatment with PFOA.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat breast or colon or prostate cancer with PFOA treatment, particularly in humans. Applicants have merely provided in vitro of possible efficacy.

Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity

of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonably degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore, it is well known in the art that cultured cells, over a period of time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York., p4) teach that it is recognized in the art that there are many differences between cultured cells and counterparts in vivo. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissues are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4., see Differences in Vitro). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is note. Yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been scientific characteristics different form those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host-tumor and cell-cell interactions.

In addition, the treatment of cancer is at most unpredictable as underscored by Gura (Science, v278, 1997, pp. 1041-1042) who discusses the potential shortcomings of potential anti-cancer agents

including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed since forma screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, column one) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds could be predictably used as a treatment for all or any cancers including breast, colon or prostate, motility as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

Determining if any particular claimed compound would treat any particular cancerous disease state would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants. As noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Applicant's Remarks

Applicant's allege that page 27, lines 15-30 provide tests for support of all cancers claimed. Applicant's allege that each of the cited articles by the Examiner are more anecdotal and argumentative and the each of the three are related in some instance with potential FDA standards with products containing Teflon®. Further, Applicant states that the examiner has cited art that PFOA might cause tumors in humans arise solely from animal experiments, primarily in rats, citing that there is doubt whether tumor causation by PFOA in rats is relevant to humans. Applicant alleges hat the cited documents deal with an alleged EPA concern over levels of PFOA and that the concerns of the EPA have no general relevance to medical efficacy. Applicant alleges that the skilled person would be aware that many medicinally useful compounds have associated cancer risks. Further, Applicant alleges that the sulphorhodamine B assay was used to test inhibition of tumor cells growth in vitro using human tumor-derived cell lines. Applicant alleges hat the examiner has not cited any references that contradict what has been reported in the specification and that the specification provides working examples that correlate directly to the claimed methods. Applicant further states that the present invention does not require undue experimentation and that the applicant need not demonstrate that the invention is completely safe. Applicant concludes that enablement is based on whether the disclosure provides support for the claims, and not for further requirements such as whether the invention will be the most effective or whether the invention meets FDA standards and that it is incumbent upon the Patent Office to explain why it doubts the truth or accuracy of any statement.

Response to Applicant's Arguments

Applicant's amendments and remarks have been carefully considered in their entirety, but fail to be persuasive in establishing error in the propriety of the present rejection.

Firstly, applicant's allegation that the references are drawn to FDA and EPA standards is irrelevant since all references clearly state that PFOA is a likely carcinogen in humans. Further, though Applicants allege that PFOA tumor formation in rats is not relevant to humans, Applicants own disclosure discloses metabolic parameters in male CR Sprague Drawley rats (page 35 of instant specification) and therefore considers the experimental system reliable. Arguendo the above, the referenced cited where in regard to carcinogenic activity of PFOA in humans and each cite it as a carcinogen for humans. The New Jersey Memorandum from Gloria Post does not conclude that the provided experiments are not relevant to humans. In fact the reference teaches that the USEPA Science Advisory Board concluded that "PFOA cancer data are consistent with the USEPA cancer guidelines descriptor likely to be carcinogenic to humans.... This conclusion was based on the following 1) existence of two positive cancer studies in animals for PFOA, 2) data suggesting that PPAR-alpha activation may not be the sole mechanism of liver carcinogenesis…" (page 7 of the cited reference). The reference therefore supports the instant rejection. The cited reference by the American Council on Science and Health, does not conclude that the tumor causation mechanism by PFOA in rats is not relevant to humans. The reference simply states that "further research is needed in order to more fully understand how PFOA acts in the [human body]." Therefore, the references are not persuasive in overcoming the rejection.

Applicant's allegation that many medicinally useful compound have associated cancer risks, is irrelevant to overcoming the instant rejection since the rejection is not based on this allegation.

Applicant has not addressed any of the references in support of the instant rejection on pages 6-7 of the instant Office Action mailed on 7/10/2008. Arguendo the above, Applicant has only provided IC50 data on Table 2, page 29 of the instant specification which in fact is not that of PFOA. Applicant states

right above the table that IC50 values of PFOA were within the 200-600 uM range without stating that what cell lines were tested and most importantly the relevance of these values (though Applicant alleges that there are working examples for treating breast cancer, colon cancer or prostate cancer). Further, though Applicant relies upon the working examples in support of the assertion that the specification provides adequate enabling direction, it remains that Applicant has failed to provide any reason or basis to extrapolate the efficacy seen in the IC50 values of Table 2 to those of PFOA. In view of the state of the art, it is clear that the skilled artisan would have been highly skeptical to extrapolate the efficacy seen in the examples to the much larger breadth of subject matter instantly claimed, in the absence of any evidence and/or reasoning to do so (which, it remains, Applicant has failed to provide). Though it appears Applicant is of the opinion that the determination of enablement of the instant application would require *routine* experimentation, it remains that the state of the art was such at the time of the invention that the high degree of unpredictability noted and recognized in the art with regard to PFOA precludes extrapolation of the results to include PFOA.

With regard to applicant's allegation that no references have been provided to "contradict" the instant specification, Examiner points to pages 5-7 where several references are provided in support of the instant rejection. Further, with regard to applicant's allegation that the applicant need not demonstrate that the invention is completely safe, the Examiner believes that the allegation is moot since FDA efficacy was not required and the rejection is based on enablement requirement and the lack of correlation of in vitro results with in vivo efficacy, the lack of predictability in the cancer treatment art and the applicant has failed to overcome the rejection for the reasons noted above.

In view of the foregoing, when all of the evidence is considered, the totality of rebuttal evidence of enablement fails to outweigh the evidence in support of the instant conclusion of a lack of adequate enabling guidance presented in the instant specification.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 9am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

/Patricia A. Duffy/
Primary Examiner, Art Unit 1645